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CORRESPONDENCE

Research Correspondence

Prodromal Angina Limits Infarct Size in the Setting of Acute Anterior Myocardial Infarction Treated With Primary Percutaneous Intervention

To the Editor: We demonstrated that prodromal angina reduces infarct size in the setting of acute myocardial infarction (MI) treated with fibrinolysis (1), and this favorably influences outcome (2). Although the mechanism(s) remain unclear, we proposed a role for ischemic preconditioning (1), while others suggested accelerated thrombolysis (3). If preconditioning plays a role, the effect should be detectable regardless of how the infarct-related artery (IRA) reperfusion is achieved, and studying patients undergoing primary percutaneous intervention (pPCI) may elucidate such role in determining myocardial protection.

Between January and August 1998, 22 patients were prospectively and consecutively enrolled if they had: 1) chest pain duration ≤6 h; 2) ST-segment elevation of ≥1 mm in two contiguous leads; 3) IRA Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 at baseline angiography and achievement of TIMI flow grade 3; 4) first acute anterior MI; and 5) new-onset prodromal angina within the previous 24 h. Exclusion criteria were hemodynamic instability or the presence of malignant arrhythmias. Symptom status before MI was checked with a questionnaire filled in by the admitting physician. A 12-lead electrocardiogram (ECG) was recorded before and 30 min after angioplasty, then daily until discharge. The sum of ST-segment elevation ($\Sigma ST\uparrow$) was measured manually 20 ms after the end of QRS complex. Infarct size was estimated from the 12-lead ECG according to a 32-point QRS system score (4). On the admission ECG, all leads exhibiting ≥100-μV ST↑ received the maximum QRS score. The sum (QRS_0) represented the extent of the area at risk, while that at seven days (QRS_7) represented the actual MI size. The "ECG salvage index" was calculated as $(QRS_0 - QRS_7)/QRS_0$. Blood samples for measuring creatine kinase (CK)-MB levels were taken on admission, and every 8 h for the first 24 h. The infarct size was estimated on the basis of the area under the curve of the CK-MB concentration plotted against time. Left ventriculography (30° right anterior oblique) was taken on baseline, before any revascularization therapy, and six months later. Ventricular volumes and ejection fraction were calculated by the area-length method, and regional wall motion analysis was performed with the centerline method (5). The area-at-risk was defined as the number of chords showing ≥2 standard deviations below the normal at the baseline, while infarct size as the number of chords with the same feature at

Table 1. Clinical Characteristics, Angiographic Data, and Ischemia Time According to the Presence of Prodromal Angina

	Angina Negative (n = 10)	Angina Positive (n = 12)	p Value
Age (yrs)	64 ± 14	60 ± 9	0.50
Gender (% male)	70	75	1.00
Smoking (%)	20	25	1.00
Hypertension (%)	32	45	0.37
Diabetes (%)	20	17	1.00
Hypercolesterolemia (%)	40	25	0.77
Previous angina >3 months (%)	40	33	1.00
Heart rate (beats/min)	79 ± 9	77 ± 12	0.62
SBP (mm Hg)	143 ± 7	154 ± 22	0.24
Killip class (>1)	20	25	1.00
No. of vessel with ≥50% stenosis (% of patients):			
1-vessel disease	90	83	1.00
>1-vessel disease	10	17	1.00
Collateral circulation to IRA	0	0	NA
Symptom onset to hospital arrival (min)	95 (68–165)	90 (71–136)	0.87
Hospital arrival to procedure initiation (min)	37 (27–45)	30 (19–37)	0.30
Procedure initiation to stable TIMI flow grade 3 re-establishment (min)	17 (15–19)	13 (6–15)	0.1
Total ischemia time (from symptom onset to stable TIMI flow grade 3) (min)	145 (125–211)	130 (98–189)	0.30
Aspirin (%)	100	100	1.00
Unfractionated heparin	100	100	1.00
Coronary stenting (%)	100	100	1.00
Abciximab (%)	40	33	0.90
Thienopyridines	100	100	1.00
Beta-blockers	70	67	0.90
ACE inhibitors	80	83	0.82

ACE = angiotensin-converting enzyme; IRA = infarct-related artery; min = minutes (median and 25th to 75th interquartile range); SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Ventriculographic Data According to Presence of Prodromal Angina Before Index Event

	Wall Motion (SD/Chord)		Recovery (%)	Area at Risk (No. of Chords)	Infarct Size (No. of Chords)	Salvage Index (%)	EF (%)	
	B	C		B	C		B	C
PA present								
1)	−3.20	−0.85	73	41	8	80	67	75
2)	−3.70	−3.07	17	58	43	26	46	55
3)	−3.25	−0.64	80	59	8	86	47	74
4)	−3.62	−0.19	95	51	5	90	34	74
5)	−3.00	−0.74	75	49	5	90	48	75
6)	−2.86	−2.55	11	44	25	43	53	59
7)	−3.05	−0.58	81	36	8	78	62	71
8)	−3.58	−2.91	81	52	35	33	44	56
9)	−3.05	−0.75	25	45	7	85	51	73
10)	−3.52	−0.13	96	46	6	87	40	72
11)	−2.95	−0.58	80	45	4	91	47	69
12)	−2.65	−2.49	9	40	30	25	51	59
Mean	−3.20	−1.28*	60†	47	15‡	64§	49	68‖
± SD	0.34	1.10	34	7	14	27	9	8
PA absent								
1)	−2.48	−2.48	0	30	30	0	76	65
2)	−3.26	−2.11	35	55	14	75	55	65
3)	−2.59	−1.13	56	30	7	77	62	75
4)	−3.91	−2.67	32	67	45	33	26	54
5)	−2.16	−1.87	13	31	21	32	64	52
6)	−2.65	−2.48	6	34	30	22	66	55
7)	−3.41	−2.35	31	50	26	48	55	63
8)	−2.80	−1.40	50	35	21	41	52	67
9)	−3.89	−2.55	34	65	48	26	29	52
10)	−2.56	−2.07	19	35	30	14	60	51
Mean	−2.97	−2.11	28	43	27	32	55	60
± SD	0.60	0.51	18	15	13	26	16	8

*p = 0.03 vs. follow-up wall motion abnormalities in patients without PA; †p = 0.01 vs. percent recovery of patients without PA; ‡p = 0.05 vs. infarct size in patients without PA; §p = 0.01 vs. salvage index in patients without PA; ‖p = 0.04 vs. six-month ejection fraction in patients without PA.
B = baseline ventriculography; C = control (i.e., six-month ventriculography); EF = ejection fraction; PA = prodromal angina.

the six-month ventriculography. The "ventriculographic salvage index" was defined as (area at risk − infarct size)/area at risk. The primary end point was the reduction of ventriculographic infarct size in patients with prodromal angina. Based on previous experience (2), to detect a 25% relative reduction of infarct size, 11 patients per group were necessary (alpha = 0.05, beta = 0.2). The data are presented as mean values ± standard deviation, if not otherwise stated. Continuous variables were analyzed with an unpaired *t* test and Mann-Whitney test. A value $p \leq 5\%$ was considered significant.

Twenty-two patients were studied; 12 (54.5%) with and 10 (45.5%) without prodromal angina. The clinical and angiographic variables are listed in Table 1. There were no differences between groups. Despite a similar QRS_0 (14.6 ± 2.2 vs. 13.4 ± 2.3, p = 0.25), patients with prodromal angina had a smaller infarct size (QRS_7: 4.5 ± 2.5 vs. 6.5 ± 2.4, p = 0.07), and a significantly better salvage index (68 ± 21% vs. 52 ± 14%, p = 0.05). The average reduction of ΣST ↑ was similar (63 ± 22% vs. 66 ± 18%; p = 0.67). The area under the CKMB curve was smaller in the prodromal angina group (3,557 ± 2,541 vs. 6,005 ± 2,965 $U^{-1-1} \cdot 24$ h, p = 0.05). Due to very short time-to-treatment, both groups improved ventriculographic parameters at follow-up, but patients with prodromal angina showed an additional 32% of myocardium at risk salvaged (95% confidence interval [CI]: 9% to 56%; $p < 0.01$), and six-month ejection fraction significantly improved (8%, 95% CI: 0.6% to 15%; p = 0.036). Details are reported in Table 2.

In this prospective study, the presence of prodromal angina before an anterior MI successfully reperfused with pPCI protects the ischemic myocardium, being associated with a smaller infarct size. Lytic agents take 45 to 60 min to reestablish blood flow; Andreotti et al. (3) reported in patients with MI preceded by prodromal angina that fibrinolysis accelerates IRA reperfusion by 21 min causing smaller infarct size. Angioplasty is not affected by a slow onset of action, and the presence of prodromal angina would not be expected to affect the rapidity of reperfusion. We, therefore, studied the protection afforded by prodromal angina on jeopardized myocytes independent of the earlier dissolution of the thrombus. Because both groups showed myocardial reperfusion, as assessed by the concomitant presence of TIMI flow grade 3 and significant reduction of ΣST ↑, and no other major baseline clinical and angiographic differences were detected, our data suggest that infarct size reduction is mainly driven by preconditioning, when total occlusion time and reperfusion adequacy are controlled for. However, prodromal angina patients achieved TIMI flow grade 3 slightly earlier, suggesting that its presence might have caused a more unstable clot structure, due to less activated platelets, as supported by experimental data (6).

Although prospective, our study reports a single-center experience in a small and highly selected patient cohort with a remarkably low-risk profile and a very short time-to-treatment. There is a conflicting evidence about the prognostic significance of prodromal angina associated with pPCI, because someone found a better outcome (7), while others not (8,9). We documented that the additional infarct size reduction associated with prodromal angina translated into better long-term ejection fraction, which could positively affect prognosis in an appropriately sized patient cohort. Differences in patient selection and study protocols (retrospective vs. prospective), as well as inconsistency of the prodromal angina definition, could also explain conflicting results.

In conclusion, in our study, prodromal angina leads to a smaller infarct size most likely through ischemic preconditioning. This might represent a clinical "marker" of myocardial viability. Larger prospective trials are needed to demonstrate whether this observation translates into a better outcome in patients receiving pPCI.

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Gender Differences in Endothelial Tissue-Type Plasminogen Activator Release in Middle-Aged Adults

To the Editor: Between the ages of 45 and 65 years, the incidence of myocardial infarction is three times higher in men compared with women. In addition, the prevalence of thrombotic stroke is ~50% greater in men than women (1). The mechanisms behind this gender difference in atherothrombotic events remain unclear. Impaired endothelial regulation of fibrinolysis, specifically reduced capacity to release tissue-type plasminogen activator (t-PA), has been linked directly to increased atheromatous plaque burden and increased coronary atherothrombosis (2,3). Endothelial t-PA release is the predominant physiologic mechanism governing endogenous fibrinolysis. Currently, it is unknown if a gender difference in endothelial t-PA release exists. If so, this may contribute to the gender-related disparity in the prevalence and incidence of atherothrombotic events in middle-aged adults. We tested the hypothesis that the capacity of the endothelium to release t-PA is greater in middle-aged women compared with men.

Sixty-six healthy sedentary adult humans ages 45 to 65 years were studied: 30 men (58 ± 1 year) and 36 women (58 ± 1 year). All subjects were nonobese (body mass index ≤30 kg/m^2), normotensive (blood pressure <140/90 mm Hg), nonsmokers, nonmedicated, and free of overt cardiovascular, metabolic, and hematologic disease, which were assessed by medical history, resting and exercise electrocardiograms, and fasting blood chemistries. The women were at least one year postmenopausal (range 1 to 32 years) and had never taken or had discontinued use of hormone replacement therapy at least one year before the start of the study. Before participation, the subjects provided written informed consent according to the guidelines of the University of Colorado at Boulder.

Endothelial release of t-PA antigen and plasminogen activator inhibitor (PAI)-1 antigen in response to bradykinin and sodium nitroprusside was determined using an isolated forearm model. Net release or uptake rates were calculated as follows: net release = $(C_V - C_A) \times (FBF \times [101 - \text{hematocrit}/100])$, where C_V and C_A represent the concentration in the vein and artery, respectively, and FBF represents forearm blood flow. The total amount of t-PA antigen released across the forearm in response to bradykinin was calculated as the area under each curve above baseline using a trapezoidal model. Bradykinin was infused intra-arterially at 12.5, 25, and 50 ng/100 ml tissue/min and sodium nitroprusside at 1, 2, and 4 μg/100 ml tissue/min for 5 min at each dose. To avoid an order effect, the sequence of drug administration was randomized. Plasma concentrations of t-PA and PAI-1 antigen were determined by enzyme immunoassay.

Differences in subject baseline characteristics and area under the curve data were determined by unpaired *t* test. Group differences in FBF and endothelial t-PA and PAI-1 release to bradykinin and sodium nitroprusside were determined by repeated measures analysis of variance. The relationships among the variables of interest were assessed by means of Pearson's correlation coefficient and linear regression analysis. Data are reported as mean ± SEM. Statistical significance was set at $p < 0.05$.

Although none of the subjects was obese, the men demonstrated higher (all $p < 0.05$) body mass (81.8 ± 1.5 kg vs. 65.4 ± 1.6 kg),